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A Mendelian randomization study on causal effects of leisure sedentary behavior on the risk of erectile dysfunction

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Abstract

Background: Erectile dysfunction has been associated with leisure sedentary behavior in several epidemiological and observational studies. However, the interpretation of these findings is difficult due to residual confounding or reverse causality.

Objectives: To explore the causal association between leisure sedentary behavior and erectile dysfunction, and to explore the underlying mechanism using Mendelian randomization.

Materials and methods: In the present study, publicly available large-scale genome-wide association studies of leisure sedentary behaviors (television watching, computer use, and driving), erectile dysfunction, sex hormones (total testosterone, bioactive testosterone, estradiol, follicle-stimulating hormone, luteinizing hormone, prolactin, and sex hormone binding globulin), biomarkers of endothelial function (C reactive protein, E-selectin, and matrix metalloproteinase 7), and psychiatric symptoms (depression and anxiety) were used to perform two-sample Mendelian randomization analyses. The inverse variance weighting method was the main method used to estimate the association, and sensitivity analyses were also performed.

Results: A greater risk of erectile dysfunction was significantly associated with a higher genetic susceptibility to leisure computer usage (odds ratio = 3.57; 95% confidence interval = 1.78–7.16; $p < 0.001$). No evidence was obtained to suggest that watching television or driving for leisure increased the risk of erectile dysfunction. No association was found between computer use and depression, anxiety, C reactive protein, E-selectin, matrix metalloproteinase 7, or other sex hormones, with the exception of follicle-stimulating hormone levels (odds ratio = 0.29; 95% confidence interval = 0.12–0.69; $p = 0.01$). No indication of heterogeneity or pleiotropy was identified by sensitivity analysis.

Discussion: Extended computer usage for leisure raised the likelihood of developing erectile dysfunction, which may be associated to lower follicle-stimulating hormone levels; however, the role of endothelial dysfunction and psychological disorders in the

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development of erectile dysfunction should not be underestimated. Moderate physical activity may help to correct the dysfunction.

Conclusion: The present study offered substantial evidence for a positive causal association between computer use and the risk of erectile dysfunction. However, a definitive causal association needs to be established by further research.

KEYWORDS
computer use, erectile dysfunction, genome-wide association study, leisure sedentary behavior, mendelian randomization

1 | INTRODUCTION

Erectile dysfunction (ED), which is a prevalent condition in men > 40 years of age, is defined as the inability to achieve or sustain a penile erection sufficient for effective vaginal intercourse.[1] It affects hundreds of thousands of men worldwide, lowering the quality of life for the sufferers and their spouses, and places a significant strain on society, economy and healthcare. Therefore, focusing on the risk factors for ED and its prevention is urgent and important. According to the different etiological factors, ED can be classified as psychogenic, organic (neurogenic, hormonal, arterial, cavernosal or drug induced), or mixed psychogenic and organic. In the past, psychogenic ED was considered to be the most common type, but several studies have confirmed that ED with organic factors accounts for > 80% of all patients.[2] In addition, altered sexual hormone levels and damaged vascular endothelial function are considered to be the two leading pathogenic causes of organic ED.[3–5]

Any activity engaged in whilst a person is awake, whether in a sitting, reclining, or lying position where < 1.5 metabolic equivalents of energy are expended is referred to as leisure sedentary behavior (LSB),[6] such as watching television, using a computer and operating a vehicle and so on.[7] Previous studies have indicated that sitting time may be positively associated with ED,[8] and erectile function could be significantly improved by the practice of physical activity.[9,10] Previous research found that if weight loss and increased physical activity were achieved, erectile function could be improved without the need for pharmaceutical intervention.[11] However, in contrast to the aforementioned studies, other reports did not find any association between ED and leading a sedentary life,[12,13] and a survey even suggested that heavy physical activity increased the prevalence of ED.[14] Such inconsistent results may be due to the failure of different studies to strictly control for confounding factors (such as age, obesity and coronary artery diseases) or the influence of reverse causality.

Mendelian randomization (MR) is an epidemiological technique aimed at unbiased detection of causal effects and, where possible, estimation of their magnitude.[15] It uses genetic variants as instrumental variables (IVs) to enhance causal inference.[16] This approach has two advantages, namely minimizing confounding and diminishing causality because genetic variants are randomly allocated at conception and cannot be modified by the development and progression of the disease. In the present study, to assess the effects of three different LSBs (television watching, driving, and computer use) on ED risk and to explore its potential pathogenesis (psychological disorders, sex hormone disorders, or endothelial dysfunction), two-sample MR analysis was performed based on data derived from large-scale, publicly available genome-wide association studies (GWAS).

2 | MATERIALS AND METHODS

2.1 | Study design

In order to estimate its causal effect on an outcome, MR studies often use single nucleotide polymorphisms (SNPs, which refer to the existence of ≥2 variants at a locus) associated with exposure as markers of genetic variation.[17] It assumes that a particular allele is robustly related to trait A, and trait A causes trait B. Unaffected by environmental factors, alleles are largely passed from parents to offspring, and individuals who inherit the allele are, in effect, being assigned a higher on-average dosage of trait A, whereas those who do not inherit the allele are assigned a lower on-average dosage. Consequently, as in randomized controlled trials (RCTs), groups defined by genotype will experience an on-average difference in exposure to trait A, whilst not differing with respect to confounding factors.[15] For SNPs to be strongly associated with exposures, three assumptions must be verified: i) The SNPs are associated with the exposure; ii) the SNPs should not be associated with unmeasured confounders of the exposure-outcome association (i.e., no horizontal pleiotropy); and iii) the SNPs should not be directly associated with the outcome except through the exposure. The second and third assumptions are collectively known as independence from pleiotropy.[18]

In the present study, LSB corresponds to trait A, while ED/sex hormone (total testosterone, bioactive testosterone, estradiol [E2], follicle-stimulating hormone [FSH], luteinizing hormone [LH], prolactin [PRL], sex hormone binding globulin [SHBG])/biomarkers of endothelial dysfunction (C reactive protein [CRP]/E-selectin/matrix metalloproteinase 7 [MMP-7] [19,20])/psychiatric symptoms (depression/anxiety) correspond to trait B. IVs for LSBs, including leisure television watching, leisure computer use and leisure driving, from a

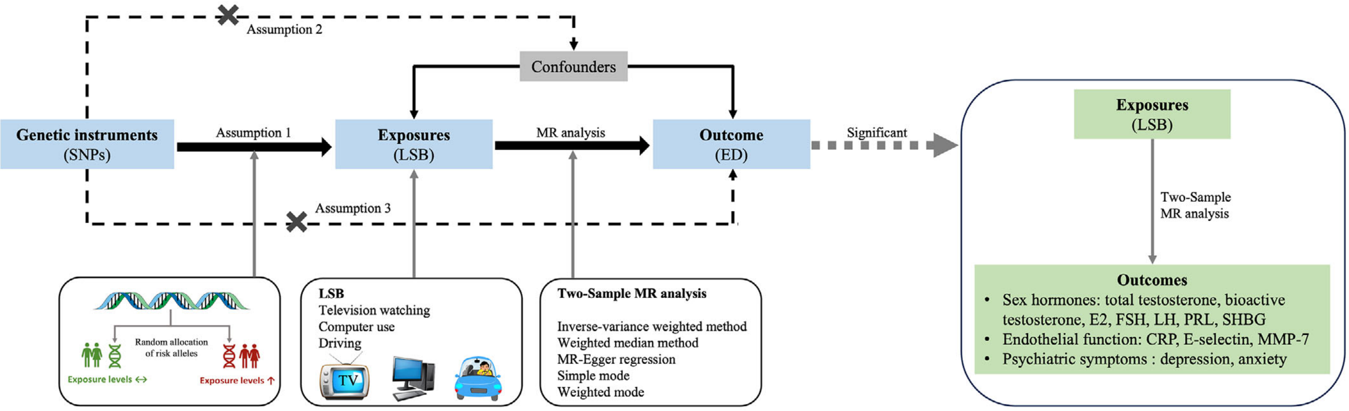


FIGURE 1 Study design overview. SNP, single nucleotide polymorphism; LSB, leisure sedentary behavior; ED, erectile dysfunction; MR, Mendelian randomization; E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL, prolactin; SHBG, sex hormone binding globulin; CRP, C reactive protein; MMP-7, matrix metalloproteinases-7.

prior study,[21] were employed to examine the causative associations between LSBs and the risk of developing ED using two-sample MR analysis. If a certain LSB was found to have a causal association with ED, MR analysis would be used again to further identify whether it affected mental state, sex hormones, or endothelial function. (Figure 1)

All GWASs included in the present study received approval from the relevant ethical boards, and participants provided signed informed consent for their enrolment in these GWASs. All data used in the present study are already available to the public, and therefore the present study did not require any further ethics approval. The GWAS articles cited in the subsequent sections contained information on the method of acquisition of such data.

2.2 | Selection of genetic IVs

The most current GWAS meta-analysis of 422,218 European participants from the UK Biobank yielded candidate genetic tools for LSB.[21] Answers to the following questions were then used to calculate the average time that each participant spent on each of the three behaviors: 'On a typical day, how many hours do you spend on watching television?'; 'On a typical day, how many hours do you spend using a computer? (Do you include using a computer at work?)'; and 'On a typical day, how many hours do you spend driving?'. The original studies indicated that participants spent an average of 2.8 h (standard deviation [SD] = 1.5 h) per day on leisure television watching, 1.0 h (SD = 1.2 h) on leisure computer use, and 0.9 h (SD = 1.0 h) on driving. After obtaining the clinical data of LSB time and SNPs in the whole genome of the study objects, the SNPs associated with LSB were screened by correlation analysis of genotype and phenotype. The previously released cohort profile contains further details about the GWAS data.[21]

Since false positive events were prone to occur when multiple comparisons of numerous gene variants were made in the aforementioned GWAS,[21] the present study used a stricter *p*-value (5×10^{-8}) to minimize the risk of irrelevant SNPs being included in the study. A total of 152, 37, and four SNPs associated with television watching, computer use, and driving, respectively, were identified at the genome-wide significance level ($p < 5 \times 10^{-8}$), and a series of screening methods were then used to further improve the criteria for the eventual inclusion of SNPs to increase the reliability and reproducibility of the findings. First, using the European population reference, linkage disequilibrium clumping with a clumping window of 10,000 kb was used, and SNPs with higher *p*-values at a threshold of linkage disequilibrium ($R^2 > 0.001$) were excluded to guarantee that IVs were independent of each other. Secondly, SNPs that were significantly associated ($p < 5 \times 10^{-8}$) with the results were eliminated. Thirdly, SNPs with missing required information were also excluded. Fourthly, the PhenoScanner v2 GWAS database (http://www.phenoscanner.medschl.cam.ac.uk) was searched for every instrumental SNP in order to identify any prior correlations with potential confounding phenotypes (including coronary artery disease and obesity), and the effects of manually eliminating these genetic variations from the two-sample MR analysis were subsequently assessed.[22–26] Fifthly, only strong IVs (F-statistics > 10) for the abovementioned three types of LSB were identified after using F-statistics to confirm the strength of the IVs. The formula $F = [R^2 \times (N-K^{-1})] / [K \times (1 - R^2)]$ was used, where K is the overall quantity of SNPs considered in the research, *N* is the number of samples used in the selected GWAS, and R^2 is the selected SNPs' cumulatively explained variance throughout the exposure.[27] Upon screening, the number of SNPs was 102 for television watching, 25 for computer use, and three for driving. The detailed process for selecting IVs is presented in Data S1. The included SNPs exhibited strong strength, with F-statistics ranging from 32 to 78 for television watching, 33 to 52 for computer use, and 37–45 for driving (Table S1). Subsequently, SNPs that were palindromic with intermediate allele frequencies, incompatible SNPs and potential outliers identified by the MR-pleiotropy residual sum and outlier test were excluded to correct horizontal pleiotropy.[28]

2.3 | Data sources for the study outcome

A prior GWAS study on European ancestry was used to extract the ED summary-level dataset.[29] Three cohorts were pooled to recruit a total of 223,805 individuals (6175 cases and 217,630 controls), giving more inference power. In order to make the diagnosis of ED, the International Classification of Diseases, 10th Edition (codes N48.4 and F52.2), a history of medical interventions for ED (such as oral medications or surgery), or self-reports from the individuals concerned were used. In addition, thorough descriptions of the outcome data sources of total testosterone, bioactive testosterone, E2, FSH, LH, PRL, SHBG, CRP, E-selectin, MMP-7, depression, and anxiety are shown in Table S2.

2.4 | Statistical analysis

The main analytical technique used in the present study was the inverse variance weighting (IVW) method of the random effects model.[30] Simultaneously, causal associations were inferred using median weighting,[31] MR-Egger,[32] simple mode, and weighted mode analyses. To assess how the effectiveness of IVs, different assumptions were made for each technique. When 50% of the IVs were determined to be invalid, median weighting was estimated.[31] After correcting for multiple effects, the MR-Egger method was suitable for providing an estimate, despite its lower statistical capabilities.[32] Irrespective of whichever type of horizontal pleiotropy existed, even if the most frequent horizontal pleiotropy value was 0, the simple mode approach was still able to offer a reliable estimate. Additionally, the weighted mode technique demanded that valid IVs provided the largest subset of instruments showing the same correlation.[33] Therefore, all these techniques were used to thoroughly analyze the causation aspects.

Several sensitivity analyses were also performed. First, heterogeneity between individual SNP estimations was evaluated using Cochran's Q test. $p > 0.05$ was considered to indicate no heterogeneity. Secondly, by using the MR-Egger intercept method, the horizontal pleiotropy of IVs was evaluated.[32] The intercept was used to assess the horizontal pleiotropic effects across the SNPs, and the IVW estimate was acknowledged to have been biased if $p < 0.05$. Thirdly, to ascertain whether a single SNP was responsible for the outcomes, a leave-one-out sensitivity test was performed. Fourthly, to pinpoint the presence of pleiotropy, funnel plots were created.

All statistical analyses were performed in the R software (version 4.2.2), using the "TwoSampleMR" and "MR-PRESSO" packages.[28,34] All *p*-values were two-sided.

3 | RESULTS

The results of IVW provided strong evidence that long-term leisure computer use was associated with a higher risk of developing ED. The odds ratio (OR) was determined to be 3.57 (95% confidence interval [CI] = 1.78–7.16; $p < 0.001$) for one SD increase of computer use time (1.2 h). However, there were no data supporting causal associations of genetically predicted leisure television watching (OR = 0.92; 95% CI = 0.64–1.32; $p = 0.64$) or leisure driving (OR = 0.59; 95% CI = 0.13–2.69, $p = 0.49$) with ED were found (Figure 2 and Table S3).

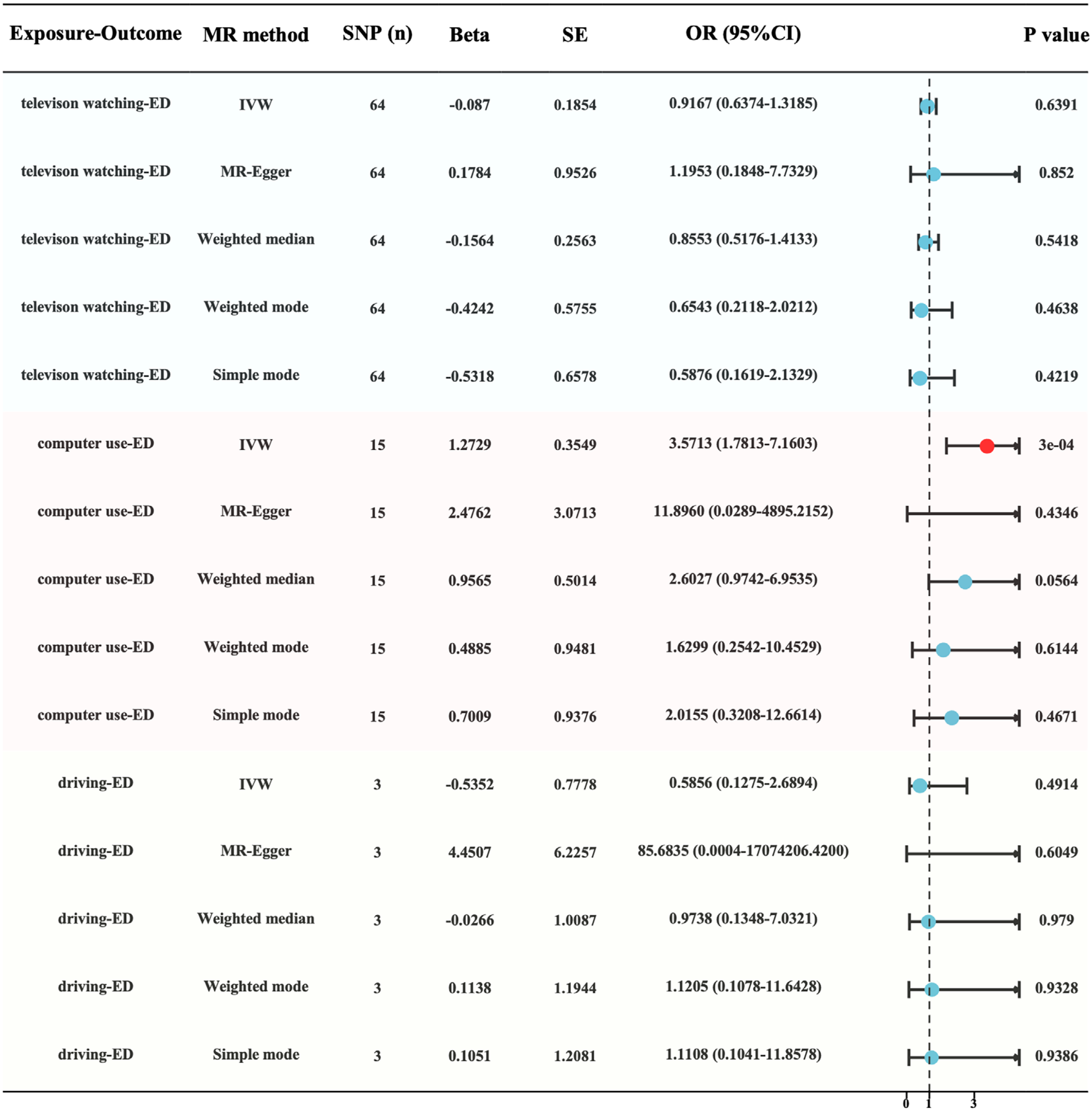
Next, the present study explored potential associations between computer use and psychological disorders/sex hormones/endothelial function. Notably, the IVW results showed no association between computer use and depression/anxiety/total testosterone/bioactive testosterone/E2/LH/PRL/SHBG/CRP/E-selectin/MMP-7, but computer use was only associated with lower FSH levels (OR = 0.29; 95% CI = 0.12–0.69; $p = 0.01$). (Figure 3 and Table S3).

Although the MR-Egger, weighted median, and weighted mode approaches did not fully support the causal association shown by the aforementioned IVW method, the IVW results were considered reliable when the slope coefficients of the above four methods were in the same direction. In addition, no indication of heterogeneity was detected using Cochran's Q test, and neither was any indication of directional pleiotropy detected using the MR-Egger regression method (Table S3). The findings of the leave-one-out analysis confirmed that no potentially significant SNP caused any significant bias in the causal connection, which reconfirmed the above conclusions (Figure S1). Furthermore, the constructed funnel plot was symmetrical, indicating that no apparent horizontal pleiotropy existed (Figure S2).

4 | DISCUSSION

In modern society, there are numerous possibilities to engage in sedentary lifestyle activities, including watching television, using a computer, or driving. In the present study, the causal connection between the aforementioned three LSBs and ED has been investigated using MR analysis. It was revealed that each 1.2 h increase in leisure computer usage predicted a 3.57-fold greater odds risk of ED. However, no causal association was detected between television watching, driving, or ED. Based on these findings, the current study also explored the potential association between computer use and major etiology or pathological mechanisms of ED (psychological factors, sex hormone disturbance, and endothelial dysfunction). The results showed a causal association between computer use and lower FSH levels, but no direct causal association with other sex hormones (total testosterone, bioactive testosterone, E2, LH, PRL, or SHBG), endothelial dysfunction biomarkers (CRP, E-selectin, or MMP-7) or psychiatric symptoms (depression or anxiety).

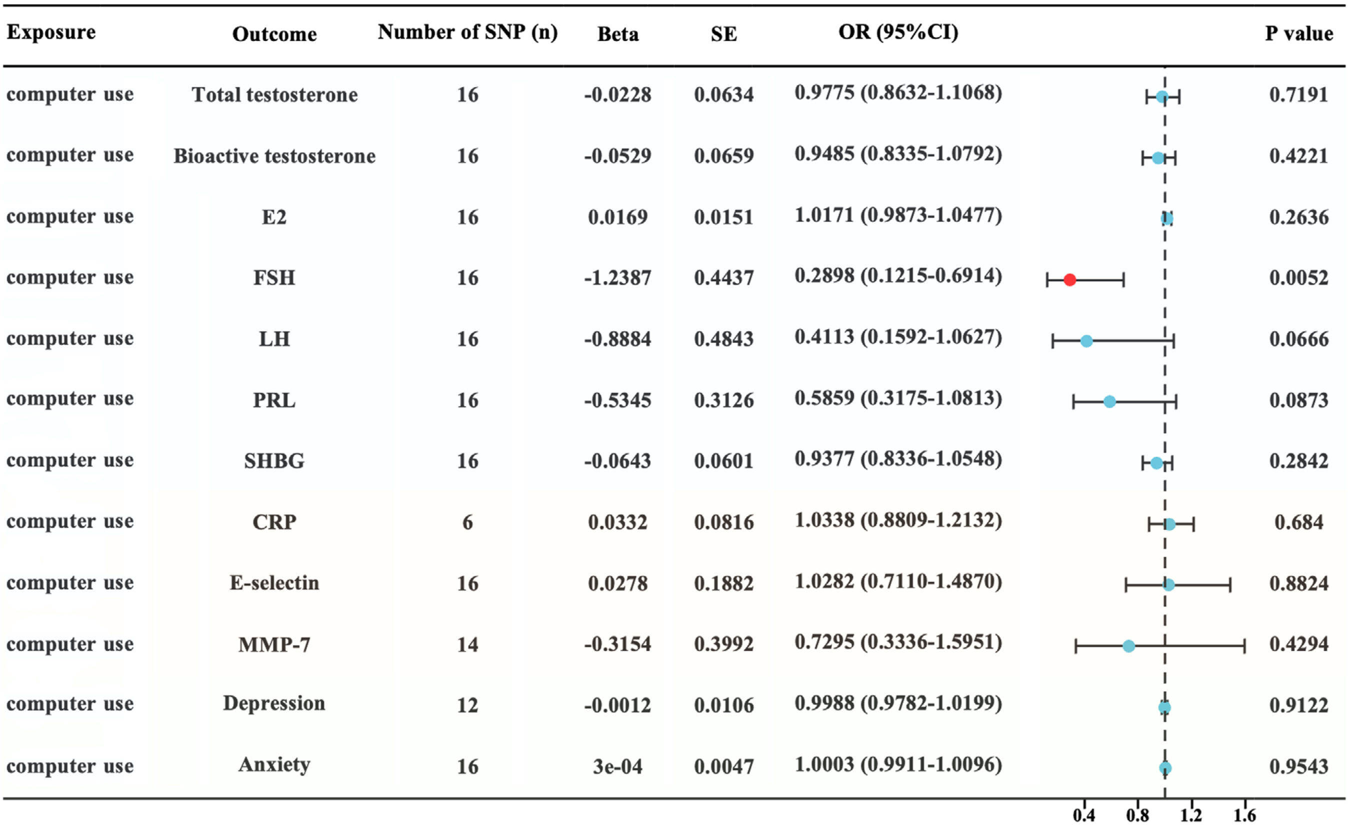
The link between lifestyle and ED has been continuously explored in the last decades, but the results have not been uniform. On the one hand, regardless of whether the subjects were > 20 or > 50 years old, some observational studies found a positive association between certain sedentary behaviors (television watching, video viewing, and computer use) and ED.[35–42] Sitting for > 9 h per day could even lead to a significant increase in the incidence of severe ED.[8] On the other hand, some studies found that a sedentary lifestyle was inversely associated with ED,[12] or was not associated with erectile function.[43–45] The causal association between computer use and ED found in the



Exposure-Outcome	MR method	SNP (n)	Beta	SE	OR (95%CI)	P value
televison watching-ED	IVW	64	-0.087	0.1854	0.9167 (0.6374-1.3185)	0.6391
televison watching-ED	MR-Egger	64	0.1784	0.9526	1.1953 (0.1848-7.7329)	0.852
televison watching-ED	Weighted median	64	-0.1564	0.2563	0.8553 (0.5176-1.4133)	0.5418
televison watching-ED	Weighted mode	64	-0.4242	0.5755	0.6543 (0.2118-2.0212)	0.4638
televison watching-ED	Simple mode	64	-0.5318	0.6578	0.5876 (0.1619-2.1329)	0.4219
computer use-ED	IVW	15	1.2729	0.3549	3.5713 (1.7813-7.1603)	3e-04
computer use-ED	MR-Egger	15	2.4762	3.0713	11.8960 (0.0289-4895.2152)	0.4346
computer use-ED	Weighted median	15	0.9565	0.5014	2.6027 (0.9742-6.9535)	0.0564
computer use-ED	Weighted mode	15	0.4885	0.9481	1.6299 (0.2542-10.4529)	0.6144
computer use-ED	Simple mode	15	0.7009	0.9376	2.0155 (0.3208-12.6614)	0.4671
driving-ED	IVW	3	-0.5352	0.7778	0.5856 (0.1275-2.6894)	0.4914
driving-ED	MR-Egger	3	4.4507	6.2257	85.6835 (0.0004-17074206.4200)	0.6049
driving-ED	Weighted median	3	-0.0266	1.0087	0.9738 (0.1348-7.0321)	0.979
driving-ED	Weighted mode	3	0.1138	1.1944	1.1205 (0.1078-11.6428)	0.9328
driving-ED	Simple mode	3	0.1051	1.2081	1.1108 (0.1041-11.8578)	0.9386

FIGURE 2 Causal estimates of leisure sedentary behaviors in ED with five MR methods. Red dots indicate a statistically significant causal relationship between exposure and outcome; blue dots indicate no statistical significance. ED, erectile dysfunction; SNP, single nucleotide polymorphism; SE, standard error; OR, odds ratio; CI, confidence interval; IVW, inverse variance weighted method.

present study strongly suggested that LSB may impair erectile function, even though the causal association between another two LSBs (television watching and driving) and ED was not found. The lack of causality may be due to the following possibilities. Since exposure data was gathered through self-report, there is a possibility of misclassification. The increasing use of streaming services makes it more difficult to distinguish between television watching and computer use; as a result, watching television on the computer may have been classified as computer use, which may explain the lack of association between television watching and ED. In addition, since specific clinical epidemiological information was not available, specific patterns of LSB (e.g., continuous sedentary behavior without rest or intermittent sedentary behavior) were not obtained. In fact, even with the same total sitting time, different patterns of sitting time may cause different harms. A previous study reported that even if the total sitting time was the same, short periods of sedentary time with intermittent physical activity could have



Exposure	Outcome	Number of SNP (n)	Beta	SE	OR (95%CI)	P value
computer use	Total testosterone	16	-0.0228	0.0634	0.9775 (0.8632-1.1068)	0.7191
computer use	Bioactive testosterone	16	-0.0529	0.0659	0.9485 (0.8335-1.0792)	0.4221
computer use	E2	16	0.0169	0.0151	1.0171 (0.9873-1.0477)	0.2636
computer use	FSH	16	-1.2387	0.4437	0.2898 (0.1215-0.6914)	0.0052
computer use	LH	16	-0.8884	0.4843	0.4113 (0.1592-1.0627)	0.0666
computer use	PRL	16	-0.5345	0.3126	0.5859 (0.3175-1.0813)	0.0873
computer use	SHBG	16	-0.0643	0.0601	0.9377 (0.8336-1.0548)	0.2842
computer use	CRP	6	0.0332	0.0816	1.0338 (0.8809-1.2132)	0.684
computer use	E-selectin	16	0.0278	0.1882	1.0282 (0.7110-1.4870)	0.8824
computer use	MMP-7	14	-0.3154	0.3992	0.7295 (0.3336-1.5951)	0.4294
computer use	Depression	12	-0.0012	0.0106	0.9988 (0.9782-1.0199)	0.9122
computer use	Anxiety	16	3e-04	0.0047	1.0003 (0.9911-1.0096)	0.9543

FIGURE 3 Causal estimates of computer use on sex hormones, endothelial function, and psychiatric symptoms (IVW methods). Red dots indicate a statistically significant causal relationship between exposure and outcome; blue dots indicate no statistical significance. IVW, inverse variance weighted method; SNP, single nucleotide polymorphism; SE, standard error; OR, odds ratio; CI, confidence interval; E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL, prolactin; SHBG, sex hormone binding globulin; CRP, C reactive protein; MMP-7, matrix metalloproteinases-7.

relative health benefits.[46] Therefore, the absence of a causal association between ED and television watching/driving was likely to be understated by the failure to stratify patterns of LSB. Furthermore, the limited number of SNPs related to driving may have resulted in reduced statistical power, making it challenging to identify meaningful associations between genetic variants and outcomes of interest.

Normal sexual function has been described as a biopsychosocial process that involves the coordination of the psychological, endocrine, vascular, and neurological systems.[47] Loss of function or disorder of any of these factors may cause ED. Therefore, ED can be classified as psychogenic, neurogenic, hormonal, arterial, drug-induced, or mixed.[3] At present, sex hormone disturbance and endothelial function impairment are considered to be the two most important pathophysiological processes in all ED types except in simple psychogenic ED, and they are closely related to sedentary behaviors or physical exercise.[3–5] The present study found an association between computer use and low levels of FSH, which was consistent with the study by Vaamonde et al. study,[48] which reported that sedentary subjects had lower levels of FSH, LH, and testosterone than physically active subjects. However, the authors suggested that FSH levels were more closely related to sperm production than to testosterone levels or erectile function.[48] In fact, although FSH does not act on stromal cells to induce them to release testosterone, it can induce the expression of the LH receptor in stromal cells to indirectly promote testosterone secretion. Therefore, when FSH levels are low, testosterone release is also affected. (Figure 4) Although the current study did not find that computer use reduced total or bioactive testosterone levels, this association with FSH levels suggested to some extent that LSB may contribute to the occurrence and progression of ED by affecting sex hormone levels. However, there may be other unknown mechanisms by which low FSH levels can impair erectile function, which needs further investigation. However, another study found that ED was unrelated to changes in testosterone, E2, LH, FSH, PRL, or SHBG based on 1,750 health questionnaires of young infertile men.[49] Given the inconsistencies of the aforementioned findings, whether the low FSH levels found in the present study due to computer use were really a key factor in causing ED remains to be confirmed by conducting large-scale clinical studies.

Although the current study did not find a direct association between computer use and the three typical biomarkers of endothelial function (namely CRP, E-selectin, and MMP-7) and the two typical psychiatric symptoms (depression and anxiety), the role of endothelial dysfunction and psychological disorders in the development of ED should not be underestimated. Previous studies showed that physically active individuals had a lower risk of mental illness and better vascular function

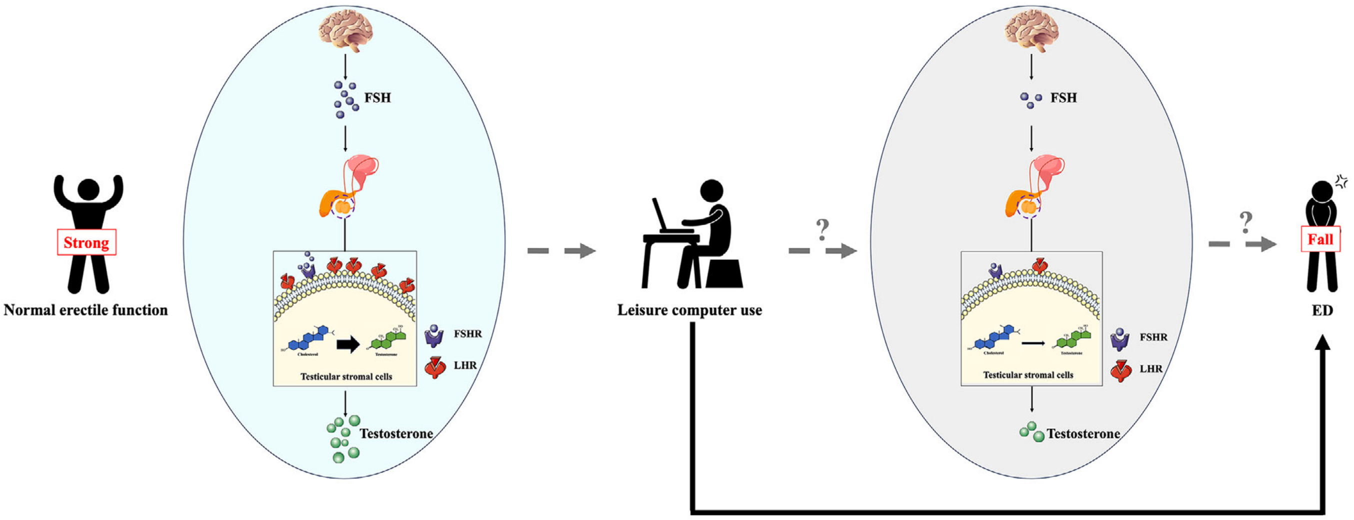


FIGURE 4 A potential mechanism that computer use may reduce luteinizing hormone receptor expression in testicular stromal cells by lowering follicle-stimulating hormone levels, thereby affecting testosterone secretion and finally leading to erectile dysfunction. The solid black arrow indicates that it has been confirmed by Mendelian randomization methods, and the gray dashed arrow indicates that it needs to be further confirmed. FSH, follicle-stimulating hormone; LH, luteinizing hormone; FSHR, follicle-stimulating hormone receptor; LHR, luteinizing hormone receptor; ED, erectile dysfunction.

than sedentary individuals. Patients with vascular ED experienced reduced endothelial cell apoptosis and improved erectile function after 3 months of moderate-to-vigorous aerobic exercise.[50] For patients with psychological disorders, physical exercise has long been considered a good adjunct therapy.[51,52] The lack of an association between endothelial dysfunction/psychiatric symptoms and computer use in the present study may be due to the small number of SNPs associated with computer use, and the fact that the current study only analyzed a few biomarkers and symptoms, since the MR analysis was limited to published GWAS data, which were not comprehensive. Computer use may also impair ED by affecting insulin resistance, production of inflammatory cytokines,[53] blood flow to the penile arteries, or endothelium-dependent vasodilation.[54] Therefore, it remains unclear whether computer use causes ED by causing endothelial dysfunction or triggering psychiatric symptoms.

Although the specific mechanism of ED caused by computer use has not been clarified in the present study, the damage of sedentary behavior to erectile function appears to be clear, which needs to attract public attention. In other words, physical activity can help to prevent ED or improve erectile function. Previous research confirmed that physical activity could not only increase the level of testosterone but also help to improve endothelial function as well as relieve depression and anxiety.[55] Lifestyle interventions alone could reduce the prevalence of ED from 66 to 44%.[11] However, the intensity and frequency of physical activity are also important to consider. Previous findings indicated that extended periods of strenuous exercise resulted in a temporary depression of various aspects of the immune function (such as neutrophil respiratory burst, lymphocyte proliferation, and monocyte antigen presentation) for 3–24 h.[56,57] Periods of intensified training (overreaching) lasting ≥1 week may result in longer lasting immune dysfunction, thus appearing various diseases or pathological states.[56,57] Therefore, physical activities must be scientifically supported and moderate. At present, there is no clear regulation on the quantity and frequency of daily physical activity required for the treatment of different severity and types of ED or the prevention of ED. Whether it is long- or short-term, and aerobic or anaerobic/resistance protocols, physical exercise is effective in improving and preventing ED,[58] but aerobic exercise with moderate-to-vigorous intensity is the most effective type of exercise for improving erection, as confirmed by previous meta-analyses studies.[13,59] However, patients with ED may also present complications related to heart diseases such as coronary artery diseases; thus, evaluation of the individual cardiovascular risk is mandatory before prescribing physical exercise to accommodate the most appropriate exercise protocol.[58] Importantly, another study has suggested that changes in lifestyle can improve erection, but only after ≥2 years, which is a markedly long time-frame.[60] By contrast, a strategy that combined oral phosphodiesterase-5 inhibitors with lifestyle changes was shown to enhance positive outcomes after 3 months.[61] Therefore, effective ED therapies should not be postponed in favor of lifestyle changes alone.

To the best of our knowledge, the present study is the first MR study on LSB and ED based on data from a large-scale consortium. The key advantage of the present MR methodology is its ability to assess the independent causal effects of LSB on ED and to explore the potential mechanisms without being influenced by reverse causality or possible confounding variables. Low levels of FSH may provide a new research direction for the pathological mechanism of ED caused by LSB. Moreover, a variety of methods were used to assess pleiotropy and heterogeneity, which ensured that the current results were free from pleiotropy and heterogeneity. Finally, the present findings may have an impact on LSB and ED healthcare policies, since knowing the causal associations that exist between LSB and ED helps to inform public health policies on early prevention of ED and prompt intervention due to the high morbidity rates of ED and the prevalence of sedentary behavior in the general population.

The present study did, however, have certain limitations. First, the limited number of available SNPs may have restricted its ability to capture the full genetic variation and detect significant associations. Secondly, since the majority of the GWAS data utilized in the present study were based on a European population, the generalizability of the conclusions may be understandably constrained, and the present findings should be verified in other populations. Thirdly, the use of genetic IVs implied that the effects of the exposures to the results would be permanent, which may not be the case in reality. Fourthly, the current study was unable to fully assess the severity and type of ED in the GWAS dataset, since it lacked raw data. Therefore, it could only be concluded that the longer the time spent using a computer, the more likely ED was to occur, but the risk of developing a specific type of ED or how severe ED would be could not be determined. Fifthly, only the IVW estimator yielded a statistically significant causality in the analysis, but, according to similar studies,[62,63] the causal association in the estimation of IVW was considered to be significant ($p < 0.05$) when the estimated direction was the same as for the MR-Egger, weighted median, weighted mode, and simple mode methods. Sixthly, the GWAS data of ED that were used in the present study only included individuals aged 40–69 years, while the incidence of ED was highest in men > 70 years of age (50-100%). Whether this result could be applied to patients aged ≥70 or < 40 years requires further investigation. Finally, due to the limitations of the database, the present study only analyzed the effects of computer use on sex hormones, endothelial function, and typical outcomes in psychiatric symptoms; however, the etiology of ED also includes neuropathic and drug-induced. Thus, although only the effects of computer use on FSH were found in the current study, the possibility of different types of ED being caused by other factors or mechanisms could not be ruled out. When more comprehensive GWAS data become available, future in-depth studies should be conducted.

5 | CONCLUSION

In conclusion, the present MR analysis offered substantial evidence for a positive causal association between computer use and risk of ED and found the effect of computer use on FSH, which may provide a new research direction for the pathogenesis of ED caused by LSB. In addition, scientifically demonstrated and moderately strong physical exercise should be done to prevent ED caused by sitting for excessive time. However, in the future, further high-quality RCTs and comprehensive mechanistic studies are necessary to establish a definite causal link between these events.

AUTHOR CONTRIBUTIONS

The study's design was created by Zhao Huangfu, Xiao Zhang, and Linhui Wang. Zhao Huangfu analyzed the data and wrote the manuscript. Data downloads were assisted by Xinxin Gan, Qingyang Pang, and Baohua Zhu. Data analysis and literature review were assisted by Xiao Zhang, Xinxin Gan, and Yiren Yang. The manuscript's published form was accepted by all authors after they had read it.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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